REMARKS

Amendments to the Claims

Claims 22, 23, and 53 have been amended, and claims 30, 31, 36-38, 42, 43, 46-48, 54 and 55 have been canceled, to point out with more particularity and clarity the subject matter regarded by Applicants as their invention.

For greater particularity and clarity, independent claim 22 has been amended to specify that the claimed anti-idiotype antibody is to an idiotype of a second antibody, "wherein said idiotype of said second antibody specifically binds to an epitope of native MN protein." [Emphasis added.] Correspondingly, the subsequent phrase "said MN protein" has been replaced with the phrase "said native MN protein" in claims 22 and 23. [Emphasis added.] Particular support for those amendments can be found in the specification at least at page 75, lines 23-25, which reads: "'Ab2 mimicking the normal antigen (so-called internal image Ab2) may be used as a surrogate antigen for vaccination to trigger the host's immune system specifically against the nominal antigen.'"

Claim 22 has been further amended to specify that the native MN protein has an amino acid sequence represented by SEQ ID NO: 2. Support for that amendment can be found at the least at page 11, lines 9-10, which reads: "A predicted amino acid sequence for a preferred MN protein of this invention is shown in Figure 1 [SEQ. ID. NO. 2]."

For increased clarity and particularity, claims 30, 31, 36-38, 42, 43, 46-48, 54 and 55 have been canceled. The independent claims of those cancelled claims, that is, claims 30 and 42, each claim

> [a]n anti-idiotype antibody to an idiotype of a second antibody, wherein said idiotype of said second antibody specifically binds to an epitope of an MN polypeptide, wherein said anti-idiotype antibody comprises an internal image corresponding to said epitope of said MN polypeptide, **wherein said epitope of said MN polypeptide is an epitope found in the MN protein encoded by SEQ ID NO: 1**. . . .

[Emphasis added.] Applicants respectfully note that the coverage in the cancelled claims in essence coextends with that of pending claims 22, 23 and 53, in that the

claimed anti-idiotype antibodies are those that antigenically mimic the native MN protein having the amino acid sequence of SEQ ID NO: 2.

Claim 53 has been amended by replacing the phrase "biologically active antibody fragment" with the phrase "antigen-binding antibody fragment" to describe the second antibody with more particularity and clarity. Support for that amendment can be found in the instant specification at the least at page 68, lines 18-20, which reads: "The term 'antibodies' is defined herein to include not only whole antibodies but also biologically active fragments of antibodies, preferably fragments containing the antigen binding regions." [Emphasis added.]

Applicants respectfully conclude that no new matter has been entered by the above amendments.

I. First 35 USC Section 112, First Paragraph Rejection (Section 9 of Office Action)

Claims 22, 30, 36-38, 42, 43, 46-48 and 53-55 stand rejected under 35 USC 112, first paragraph because "the specification does not enable any person skilled in the relevant art to which it pertains . . . to make or use the invention commensurate in scope with the claims. . . ." [Office Action, pages 3-4.] Applicants respectfully traverse.

The Office Action at the end of section 9 at page 8 acknowledges:

> Applicant is enabled for anti-idiotypic antibodies of the beta type (i.e., $Ab_2\beta$ or internal image) to an idiotype of a scond antibody that specifically binds to an epitope of the native MN protein of SEQ ID NO: 2 that is encoded by SEQ ID NO: 1 or encoded by polynucleotides that differ from SEQ ID NO: 1 due to the degeneracy of the genetic code.

Applicants respectfully point out that the amendments to the pending claims explicitly word for word are in concert with the above-quoted concluding statement of section 9 of the office action.

Applicants, however, would be remiss if they did not respectfully point out that an epitope of the full-length MN protein of SEQ ID NO: 2 can also be found on MN protein fragments, so that, for example, now canceled claim 30 which indicates that said epitope of said MN polypeptide is an epitope found in the MN protein encoded by SEQ ID NO: 1" is claiming the same anti-idiotypic antibodies as claimed in claim 22. The

only difference from now cancelled claim 30 and claim 22 is that the MN protein of now cancelled claim 30 could have been identified as having the amino acid of SEQ ID NO: 2 (that is, the amino acid sequence encoded by SEQ ID NO: 1), and could also be encoded by polynucleotides that differ from SEQ ID NO: 1 due to the degeneracy of the genetic code.

Applicants respectfully submit that the claim amendments remove any potential lack of clarity or of particularity in regard to the subject matter regarded by the Applicants as their invention and overcome any confusion upon which the subject 112, first paragraph rejection could have been based. Applicants respectfully request that the Examiner reconsider and withdraw the instant rejection in view of the enhanced clarity and particularity provided by the above claim amendments.

II. 37 CFR Section 1.75(c) Objection (Section 10 of Office Action)

Claims 47 and 48 stand objected to under 37 CFR 1.75(c), "as being of improper dependent form for failing to further limit the subject matter of a previous claim. . . . [C]laims 47 and 48 do not include every limitation of the claim on which they depend." [Office Action, page 8.] Applicants respectfully submit that the instant objection is now moot, as the claims objected to (claims 47 and 48) have been canceled.

However, Applicants for the record respectfully point out that the instant objection is improper, as according to 35 USC 112, fourth paragraph, "[a] claim in a dependent form shall be interpreted to incorporate by reference all the limitations of the claim to which it refers." Therefore, a dependent claim by definition includes every limitation of the claim on which it depends. "[S]aid nucleic acid" of claims 47 and 48 must by definition contain "at least 29 nucleotides" and "at least 25 nucleotides," respectively.

Applicants respectfully request that the Examiner withdraw the instant 37 CFR 1.75(c) objection.

III. 35 USC Section 112, Second Paragraph Rejection (Section 11 of Office Action)

Claims 22 and 53-55 stand rejected under 35 USC 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." [Office Action, page 9.] Applicants respectfully submit that the amendments to the claims overcome the instant rejection.

a. The Office Action states: "Claim 22 recites the limitation 'said MN protein'. There is insufficient antecedent basis for this limitation in the claim. . . . Further, SEQ ID NO: 1 encodes the MN protein and not an MN protein epitope as recited." Applicants point out that claim 22 has been amended to replace the phrase "an MN protein epitope" with the phrase "an epitope of native MN protein". Therefore, Applicants submit that there said rewording provides a sufficient antecedent basis for the phrase "said native MN protein".

b. The Office Action continues in section 11(b) stating: "Claims 53-55 are indefinite in the recitation of 'biologically active antibody fragment' because it is unclear what biological activity is contemplated by the phrase." [Office Action, page 9.] For greater clarity and particularity, Applicants have cancelled claims 54 and 55, and amended claim 53 to recite "antigen-binding antibody fragment" instead of "biologically active antibody fragment".

Applicants respectfully submit that the above-identified claim amendments address the two aspects of the instant rejection, and respectfully request that the Examiner withdraw the instant rejection.

IV. Second 35 USC Section 112, First Paragraph Rejection (Section 12 of Office Action)

Claims 22, 30, 36-38, 42-43, 46-48 and 53-55 stand rejected under 35 USC 112, first paragraph,

as failing to comply with the written description requirement.

. . . .

> . . . The genus of proteins encoded by polynucleotides that differ from SEQ ID NO: 1 due to the degeneracy of the genetic code may have very different structures and functions than the MN protein of SEQ ID NO: 2. . . .

[Office Action, pages 9-11.] Applicants first respectfully point out that the MN protein encoded by SEQ ID NO: 1 and by polynucleotides that only differ from SEQ ID NO: 1 due to the degeneracy of the genetic code is the same MN protein, that is, the one with the amino acid sequence of SEQ ID NO: 2.

Applicants then respectfully submit that the above claim amendments avoid any potential lack of particularity or of clarity upon which the subject rejection could have been based, and are explicitly consonant with that that the Office Action acknowledges in the second paragraph at page 12 to meet the written description requirement of 35 USC § 112, first paragraph, that is,

> the MN protein of SEQ ID NO: 2, encoded by polynucleotides that differ from SEQ ID NO: 1 due to the degeneracy of the genetic code and encoded by SEQ ID NO: 1 . . . meets the written description provision of 35 U.S.C. § 112, first paragraph.

[Office Action, page 12, 2nd ¶.] The MN protein epitopes of claims 22, 23 and 53, and for that matter of the now cancelled claims, are those that can be found in the MN protein that has the amino acid sequence of SEQ ID NO: 2, as shown in Figure 1.

Applicants respectfully request that the Examiner reconsider and withdraw the instant 35 USC § 112, first paragraph rejection.

Two 103(a) Rejections

Applicants respectfully submit that due to questions that the Applicants have about the nature of the two 103(a) rejections of sections 13 and 14 of the instant Office Action that some prefatory remarks are felt necessary before addressing the particular details of the two instant 103(a) rejections. Applicants sincerely regret any repetition of arguments occasioned by the following exploration of the 103(a) rejections in order to address each point therein.

Legal Basis Questions

Applicants respectfully but frankly find the subject 103(a) rejections inexplicable, and are unable to determine the legal basis upon which the 103(a) rejections are made. The Office Action at page 3 withdraws two 103(a) rejections based on the same references as in the two 103(a) rejections of the instant Office Action. Applicants respectfully cannot differentiate the 103(a) rejections withdrawn by the instant Office Action from the 103(a) rejections made in the instant Office Action in sections 13 and 14.

Particularly, Applicants respectfully find the following statements from page 16 of the Office Action inexplicable and would appreciate some enlightenment from the Examiner concerning their meaning and relevance:

> Applicant's response filed 6/15/05 has been carefully considered, but is deemed not to be persuasive. The response argues the enablement of the G 250 antibody (G 250 hybridoma not deposited until September 2001) (see pages 35-43 of the response filed 6/15/05). **In view of the new rejection set forth above these arguments are not relevant to the instant rejection and, it is noted that the features upon which applicant relies (i.e., G 250 monoclonal antibody) is not recited in the rejected claims**. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants respectfully are baffled by those statements since they did not rely on "features" concerning the G250 mab in any way, wonder how the "new rejection" differs from the prior 103(a) rejections, and to what "limitations from the Specification" that the Examiner is referring. [A review of the cited *Van Geuns* case provided no further insight into the meaning of the above statements.] Again, the Oosterwijk et al., 1986 and 1988 references teach away from the instant invention and anything to do with the MN protein, MN-specific antibodies, and anti-idiotypic antibodies to antibodies that are specific to MN protein epitopes.

Perhaps, the Office Action suggests that the Applicants' prior agreements were based only on enablement, but Applicants respectfully counter that the Oosterwijk

references are not only nonenabling, but teach away from any MN-related invention, including the subject invention, and certainly provide no written description that would lead one of skill in the art to any MN-related invention. Those arguments have been made in the prior responses and will be made again infra.

Hindsight

Legion are decisions from the U.S. Supreme Court, the Federal Circuit and from lower courts, that warn against and criticize the improper use of hindsight. [For example, Yamanouchi Pharmaceutical Co., Ltd. v. Danbury Pharmaceutical Inc., 56 USPQ2d 1641, 1645 (Fed. Cir. 2000) ("as the district court aptly concluded, this case 'has all the earmarks of somebody looking at this from hindsight.'"); *In re* Kotzab, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) ("A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field."); Kahn v. General Motors Corp., 45 USPQ2d 1608, 1613 (Fe. Cir. 1998), *cert. denied*, 525 U.S. 875 (1998) ("Obviousness may not be established using hindsight."); Arkie Lures, Inc. v. Gene Larew Tackle, Inc. 43 USPQ2d 1294, 1296 (Fed. Cir. 1997) ("Good ideas may well appear 'obvious' after they have been disclosed, despite having been previously unrecognized."); Uniroyal Inc. v. Rudkin-Wiley Corp., 5 USPQ2d 1434, 1438 (Fed. Cir. 1988), *cert. denied*, 488 U.S. 825 (1988) ("The obviousness standard, while easy to expound, is sometimes difficult to apply. It requires the decision maker to return to the time the invention was made."); Bayer AG v. Sony Electronics, Inc., 229 F.Supp.2d 332, 354 (D. Del. 2002) (PITFALL: "In conducting an obviousness analysis, the Court must be mindful of the pitfall that the Federal Circuit has termed '**hindsight syndrome**'"); Smith Industries Medical Systems Inc. v. Vital Signs Inc., 45 USPQ2d 1512, 1516 (N.D. Ill. 1997), *rev'd and remanded*, 51 USPQ2d 1415 (Fed. Cir. 1999) ("In performing the task of determining obviousness, the court must imagine itself as one of ordinary skill in the art, remove the benefit of hindsight and pretend that it has never seen the invention. After familiarizing itself with the prior art, the court should ask if the invention would have been obvious, looking at the invention as a whole.").

In Gillette Co. v. S.C. Johnson & Son, Inc. 16 USPQ2d 1923 (Fed. Cir. 1990), the well known and beloved patent law scholar, Judge Rich noted that hindsight's inappropriateness as an obviousness test was discovered, and articulated lucidly, over three centuries ago, by Milton, who, in Paradise Lost, Part IV, L. 478-501, stated, in dictum (at page 1929):

> The invention all admired, and each how he
> To be the inventor missed; so easy it seemed,
> Once found, which yet unfound most would have thought,
> Impossible!

Oosterwijk et al. would have loved to have discovered the MN protein and have been the inventors of all the various MN-related inventions, including the instantly claimed anti-idiotypic antibodies, and were disappointed to find out that the instant Applicants identified the MN protein years before Oosterwijk et al. were able to identify the G250 protein. The very fact that it took many years for Oosterwijk et al. to identify the G250 antigen is in itself evidence of the nonobviousness of the instant invention.

One then examining claims for their patentability must avoid the "hindsight syndrome" so criticized and excoriated by the courts. Applicants then respectfully question why the Examiner has been citing two non-prior art references – Pastorek et al. 1994 and Uemura et al. 1999 – in 103(a) rejections in combination with Oosterwijk et al. 1986 and 1988 and the Raychaudhuri et al. '202 patent. Applicants respectfully theorize **if** one of skill in the art would have been able to follow the conventional methods used by Oosterwijk et al. to produce mabs, and that those mabs were only MN-specific, or **if** Oosterwijk et al. would lead one to identify MN-specific mabs, that then the non-prior art references would then be evidence that G250 and MN were just different names to identify the same protein. However, that is far far from the case as explained in detail below and in prior responses.

Perhaps, the Examiner is applying the non-prior art references "as evidence," because the Examiner is not just encompassing in the 103(a) rejections printed publications, but some other form of prior art that has not been identified. Applicants respectfully submit that such other form of prior art must be identified, or its aura must be eliminated from the 103(a) rejections.

That aura appears in the perception that the Office Action is referring to the G250 monoclonal antibody (mab) as if itself, its 3-D being, were part of the prior art. Applicants respectfully question whether the Examiner is basing the rejection not on the cited prior art written descriptions but on another basis. That is, is the Examiner suggesting that the G250 mab

> was known or used by others in this country . . . before the invention thereof by the applicant for patent, or
>
> (b) . . . in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States. . . .

[35 U.S.C. § 102(a) and (b).] If not, then there is no basis for discussing the G 250 mab, other than as it was described in the Oosterwijk et al. 1986 and 1988 references. Its 3-D molecular identity is not prior art, and no "evidence" of what it was years later is anything but impermissible "hindsight" that cannot be used to change the written descriptions of Oosterwijk et al. 1986 and 1988, which the Examiner has admitted to be nonenabliing [Office Action, page 3, sections 7 and 8] and which, as pointed out with great detail in Applicants' prior responses, teach away from the claimed invention.

35 U.S.C. § 103 requires that the invention be obvious "at the time the invention was made," not after the invention is disclosed. 35 U.S.C. 103(a) reads in pertinent part:

> (a) A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. . . .

[Emphasis added.] Applicants respectfully submit that abundant evidence has been supplied in Applicants' earlier responses that the identity of the MN protein was not obvious to those of the skill of the art at the time it was discovered, and that certainly antibodies specific to the MN protein and further the claimed anti-idiotypic antibodies were not obvious. The very named inventors of Oosterwijk et al., WO 88/08854, who founded the Wilex Company, which is marketing the G250 monoclonal as a cancer therapeutic, after unsuccessfully opposing the instant Applicants' European patent that

claims MN-specific antibodies, admitted the non-obviousness of MN-related inventions by taking a sub-license to Applicants' European patent and to many other of the Applicants' MN patents.

The Oosterwijk et al. inventors were in the unique position of knowing whether the G250 monoclonal had been publicly available, in public use or on sale during the critical time period, and were financially motivated to provide evidence of such public availability, public use or sale. Oosterwijk et al. did not provide such evidence in the above-identified European opposition. Further evidence that the G250 mab had not been publicly available, in public use or on sale in the critical time period is the fact that just two years ago, Oosterwijk et al. filed a U.S. patent application with claims to the now deposited hybridoma, which produces the G250 mab, to methods of producing the G250 mab, and to the use of G250 mab for cancer therapy.

Applicants respectfully submit that there is no evidence whatsoever that the G250 mab was publicly available, in public use or on sale prior to the making of the claimed invention or more than one year before the instant application's earliest priority date, and that the only evidence of the G250 mab's having been made publicly available is the deposit of the hybridoma that produces the G250 mab on September 11, 2001, that is, over nine years after the Applicants' earliest priority date.

Applicants respectfully conclude that any "aura" of the G250's 3-D availability needs to be removed from the subject 103(a) rejections, that only the written descriptions of the cited prior art references can be relied upon as a basis of the rejections, and that the use of the non-prior art references – Pastorek et al. 1994 and Uemura et al. 1999 -- in combination with the actual prior art references is impermissible hindsight. Applicants respectfully further conclude that once the 103(a) rejections are so clarified, that it is then clear that the claimed invention was non-obvious at the time it was made.

References Cited in Two 103(a) Rejections

The Office Action cites the following references in the two 103(a) rejections of Sections 13 and 14:

Oosterwijk et al., WO 88/08854 (Nov. 17, 1988) ["Oosterwijk et al. 1988"];

Oosterwijk et al., Int. J. Cancer, 38: 489-494 (1986) ["Oosterwijk et al. 1986"];

Raychaudhuri et al., U.S. Patent No. 5,270,202 (filed March 12, 1991) ["Raychaudhuri et al. '202 patent"];

Uemura et al., Brit. J. Cancer, 81(4): 741-746 (1999) ["Uemura et al. 1999"]; and

Pastorek et al., Oncogene, 9: 2877-2888 (1994) ["Pastorek et al. 1994"]

To avoid repetition in the context of each of the two 103(a) rejections of Sections 13 and 14 of the Office Action, each of the references will be discussed individually to show that each of the references is either simply not prior art to the claimed invention, or evidences the nonobviousness of the claimed invention. Applicants respectfully submit that the references individually or in any combination cannot therefore render the instantly claimed invention obvious.

Pastorek et al. 1994 and Uemura et al. 1999

Applicants respectfully submit that Pastorek et al. (1994) and Uemura et al. 1999) published long after the earliest priority date of the instant application, are simply not prior art references. As explained above, it is impermissible hindsight to combine either Pastorek et al. 1994 and/or Uemura et al. 1999 with any prior art references to attempt to provide a basis of obviousness against the claimed invention.

Oosterwijk et al 1986 and 1988 ["Oosterijk References"]

Oosterwijk et al. 1986 and 1988 discuss the following biological materials:

- 5 monoclonal antibodies ("mabs") to renal cell carcinomas ("RCCs"), one of which is a monoclonal antibody ("Mab") termed "G250"
- 5 antigens associated with RCC, one of which is an antigen termed "G250"
- hybridomas secreting the above 5 monoclonal antibodies.

The Oosterwijk references do not describe how to reproducibly obtain the G250 Mab, as they insufficiently disclose the antigen to which the G250 Mab binds. The Oosterwijk references provide no biochemical characteristics about the G250 antigen. Oosterwijk et al. 1988 at page 18, lines 15-16 "suggests that G250 recognizes a protein." [Emphasis added.] A document can only be considered as relevant state of the art if it describes a technical teaching that can be reproduced properly by one of skill in the art.

Such a technical teaching on how to reproducibly obtain the G250 Mab is not so disclosed in the Oosterwijk references.

Further and most importantly, the Oosterwijk references teach away from any MN-related invention. The only characterization of the G250 antigen that is supplied in the Oosterwijk references is what could have been deduced from the immunoreactivity of the G250 Mab. **However, the immunoreactivity of the G250 Mab as reported by the Oosterwijk references is distinctly different from the immunoreactivity of the MN-specific antibodies of the present invention.**

Whereas the Oosterwijk references describe the G250 Mab as basically being specific to kidney carcinoma [i.e., renal cell carcinoma (RCC)], and having low or no reactivity with cancers of most other organs, the MN-specific antibodies of the present application are strongly associated with cancers of many different organs. [Compare, for example, Oosterwijk et al. 1988 at page 7, lines 7-10 with the present application at page 2, line 29 to page 3, line 21 (cervical and colorectal lesions)]. **Further, Oosterwijk et al. 1988 indicates that if the G250 Mab stained non-RCC tumor cells, the staining was cytoplasmic [page 18, lines 27-29], but the staining of RCC tumor cells was membranous [page 19, lines 22-27]. In contrast, the present application at page 19, lines 1-2 discloses that the MN protein is "located at the cell surface, although in some cases it has been detected in the nucleus."**

Only in 1997, years after the priority date of the present application, and further years after the M75 Mab of claim 23 of the present application became publicly available from an international depository, did the inventors/authors of the Oosterijk et al. references and Uemura et al. report that the G250 antigen "is identical to MN, a tumor-associated antigen identified in **cervical carcinoma** (Pastorek et al. 1994). This antigen (G250, MN) is a transmembrane glycoprotein of 54/58 kDA and detectable in several types of malignancies. . . ." [Uemura, J. Urology 157: 377 (1997); emphasis added.]

Whatever characterization of the G250 antigen, that could have been deduced from the immunoreactivity of the G250 mab reported in the Oosterwijk references is very different from the characterization of the MN protein disclosed in the

Applicants' earliest U.S. priority patent. [Zavada et al., U.S. Patent No. 5,387,676 ("the '676 patent"] and in the instant application. Oosterwijk et al. admit in 1997 in the above quote that the G250 antigen is a "tumor-associated antigen identified in cervical cancer [by Zavada et al.]" and is a "**transmembrane glycoprotein** . . . detectable in several types of malignancies." [Emphasis added.] However, **Oosterwijk et al. 1986 and 1988 describe the immunoreactivity of the G250 mab as predominantly RCC-specific, having low or no reactivity with most other malignancies, and staining the membranes of only RCC tumor cells, and if staining at all non-RCC tumor cells, staining the cytoplasm of such non-RCC tumor cells.**

The Oosterwijk references cannot anticipate or render obvious the claims of the present application since the **G250 antigen is, not only, not identified therein by any biochemical characteristics, but also whatever characterization that could be deduced about the G250 antigen from the G250 mab's immunoreactivity reported in the Oosterwijk references is very different from the actual characterization of the MN protein disclosed in Applicants' '676 patent and in the instant application.**

Not only do the Oosterwijk references not provide an enabling disclosure of the G250 antigen, but they also provide substantially incorrect indications concerning the potential identity of the G250 antigen. One of skill in the art relying upon the Oosterwijk references would not associate the G250 antigen with the MN protein, the Oosterwijk references then cannot anticipate nor can they render obvious the claims of the present application, alone or in any combination with other prior art reference.

In Oosterwijk 1988, an antigen named G250 is described as "present on RCC . . . and absent from . . . most malignancies." [Page 2, lines 12-16.] Oosterwijk 1988 states that "[t]he sensitivity to proteinase K suggests that G250 recognizes a protein." [Page 28, lines 15-16; emphasis added.] **As indicated above, the Oosterwijk references do not even clearly identify the G250 antigen as a protein, and certainly does not provide any inkling of what the amino acid sequence of that protein would be, if it were a protein.** Further, the Oosterwijk references provide no biochemical characterization of the G250 antigen whatsoever – no isoelectric point, no

molecular weight, no indication of whether the antigen is glycosylated or not – **no biochemical characteristics at all.**

Oosterwijk et al. were not able to identify the G250 antigen until long after the publications of Zavada et al. made information regarding the MN protein and MN-specific antibodies publicly available. To summarize, **the antigen G250 is not reproducibly described by the Oosterwijk references for one skilled in the art and therefore not sufficiently disclosed, and Oosterwijk et al. teach away from correctly identifying a mab comparable to the G250 mab.**

Disclosure of the monoclonal antibody G250

Conventional methods were used to produce the G250 hybridoma, that secretes the G250 mabs as described in Example 1 of Oosterwijk et al. 1988 as well as in Oosterwijk et al. 1986: a mouse was immunized with cell homogenates from primary RCC lesions. The spleen cells were isolated and fused with Sp2/0 myeloma cells. Hybridomas were selected by picking up spots on a RCC coated filter and were grown in suspension. "Tissue culture medium from these clones was tested on cryostat sections of RCC lesions and normal kidney. Clones reacting with RCC and not with normal kidney tissue were subcloned and tested on other normal tissues." [Oosterwijk et al. 1988, p. 16, lines 7-11.]

At any one time, perhaps about 100,000 proteins are being expressed in a cell, and thousands of proteins are being expressed on the surface of a cell. There were then sure to be a great number of antigens in the cell homogenate used for immunization in the above process. Further, the G250 antigen would be expected to have several different epitopes. **It is obvious that the above method of producing hybridomas and screening antibodies would produce a very large spectrum of different antibody secreting hybridomas.**

Oosterwijk et al. 1986 also state on page 493 (col. 2) that **"endogenous or exogenous retrovirus expression in RCC . . . may explain the relatively large number of new antigens in RCC."** [Emphasis added.] The described process for the production of a G250 hybridoma does not enable the skilled artisan to determine, to

which of the huge number of antigens in RCC cell homogenates the secreted G250 mabs are specific.

Further, Oosterwijk et al. 1986 supports that there are a wide variety of mabs that stain RCC but do not stain normal kidney tissue. In Oosterwijk et al. 1986, it is stated that the G250 mab recognizes an antigen preferentially expressed on cell membranes of RCC and not expressed in normal proximal tubular epithelium. In the discussion [see page 493], Oosterwijk et al. 1986 cite to several other references. All of those references deal with mabs developed against RCC. Oosterwijk et al. 1986 noted that "it is seen that only antibodies S22 . . . [Ueda et al., PNAS (USA), 78(8): 5122-5126 (Aug.1981)], D5D . . . [Vesella et al., Cancer Res., 45: 6131-6193 (Dec. 1985)], and B7, C8, D8 and E6 . . . [Schärfe et al., Eur. Urol., 11: 117-120 (1985)] stain RCC, while they do not stain normal proximal epithelium."

In their 1986 article, Oosterwijk et al. distinguish the G250 mab from the other RCC-specific mabs that do not react with normal renal tissue only by the staining patterns of the various mabs. For example, Vesella et al.'s D5D mab stained 14 of 19 RCC (74%) in contrast to the G250 mab which stained 53 of 55 RCC (98%), and Schärfe's mabs, although staining as high a percentage of RCC as the G250 mab, do not stain sarcomatous RCC in contrast to the G250 mab [see page 493, top of column 2.]

From the foregoing, it is clear that Oosterwijk et al. do not reproducibly disclose the true nature of what they call the "G 250 mab". The authors were unable to draw a clear dividing line between the above-mentioned mabs and the G250 mab.

Oosterwijk et al. in "Immunohistochemical Analysis of Monoclonal Antibodies to Renal Antigens: Application in the Diagnosis of Renal Cell Carcinoma," Am. J. Pathol., 123(2): 301-309 (May 1986) (IDS submitted on 10/17/01) at page 307 (column 2) discuss mabs to RCC -- RC3, RC 38, RC 69 and RC 154 -- which mabs are claimed in the Oosterwijk et al. application (WO 88/08854). That article refers to "[o]ther investigators [who] have also described Mabs with a high specificity for RCC. . . . [citations admitted]," and **admit that "[a] comparison between the Mabs described in this study with Mab's against renal antigens described by others is difficult,**

partly because of different assay methods." **[Emphasis added.] If it is difficult to distinguish RCC-specific mabs from one another by their staining patterns, what would the staining pattern of a RCC-specific mab suggest about another mab that was known not to be RCC-specific and to have otherwise very different immunoreactivity than that reported for the RCC-specific mab?**

From the foregoing, **it is clear that the Oosterwijk references do not reproducibly disclose the true nature of what they call the "G 250 mab"**. All the claims of Oosterwijk et al. 1988 are directed to RCC; cancer of no other organ is mentioned in the claims. The title of Oosterwijk et al. 1988, "Monoclonal Antibodies to Renal Cell Carcinoma" highlights the RCC-specificity of the G250 mab.

A deposit of the hybridoma that secretes the G250 mab with a recognized depositary institution might have provided enabling disclosure of its nature. No such deposit occurred in conjunction with the Oosterwijk et al. 1988 application. The Examiner of the Oosterwijk et al. 1988 application indicated on page 3 of the first Communication that " . . . the monoclonal antibody producing hybridomas of the application are not deposited and thereby not reproducible. . . . In this respect, the application does not fulfill the requirement of Article 83 regarding the disclosure of microorganisms as set out in Rule 28 EPC."

From the foregoing, it is clear that the subject matter of the Oosterwijk references are not sufficiently disclosed, enabling the skilled artisan to carry out their teaching. Not only do the Oosterwijk references not anticipate or render obvious the claimed invention, alone or in conjunction with any other prior art reference, those references teach away from the identity of the G250 antigen with the MN antigen as shown above.

Figure 3 of **Oosterwijk et al. 1986** does show that the G 250 MAb stained some tumor types other than RCC. However, in non-RCC tumors "the fraction of tumors stained, the percentages of G 250-positive tumor cells and the intensity of staining were generally much lower." [Oosterwijk et al. 1986, page 492, column 1, first full paragraph.] Also, as in the Oosterwijk et al. application WO 88/08854, Oosterwijk 1986 indicates that if the **G250 Mab stained non-RCC tumor cells, the staining was always cytoplasmic** [page 492, column 1, first full paragraph], but the staining of RCC

tumor cells was membranous [page 490, column 2, last full paragraph]. The present application, however, discloses that the MN protein is "located at the cell surface, although in some cases it has been detected in the nucleus." [Instant application, page 19, lines 1-2.]

Although **Oosterwijk et al. 1988** does note at page 6, lines 17-26 that "the G250 determinant was also found in nonRCC tumors" and that G250 stains a variety of other tumors, although at low incidence. . . ." [emphasis added.], it reports at page 18, lines 24-27, that the fraction of non-RCC "tumors stained, the percentage of G250 positive tumor cells and the intensity of staining were generallly [*sic*] much lower [than in RCC]."[1] Oosterwijk et al. 1988 then lists at page 19, lines 1-9 the following non-RCC tumors that had no reactivity with the G250 mab – two Wilm's tumors, one prostatic carcinoma, five gastric carcinomas, and two liver cell carcinomas.

Oosterwijk et al. at page 18, lines 27-28 state: "The staining of positive non RCC tumor cells always appear to be cytoplasmatic." [Emphasis added.] Then, at page 19, lines 11-13 reports: "In two renal adenomas . . . all cell membranes were stained."

Those quotes from Oosterwijk et al. 1988 indicate that if stained with the G250 mab, the staining of non-RCC tumor cells was cytoplasmic, whereas the staining of renal cancer cells was membranous. In contrast, the present application as indicated above states that the MN protein is located on the cell

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1. The paragraph bridging pages 4-5 of Oosterwijk et al. 1988 describes the bar histogram of Figure 4 showing the results of staining a number of malignant tumors with the G250 mab. Whereas Figure 4 shows 90% and 63% of the RCC, primary and metastic tumor cells, respectively, to have 50% or more of the tumor cells stained, only 8% of colonic cancers, 5% of sarcomas, 5% of ovarian cancers and no mammary, pulmonary, testicular or melanoma cancers showed such staining.

   The results of staining the metastases of non-RCC tumors are not shown in Figure 4, but are described in Oosterwijk et al. 1988 at page 5, lines 6-12: "The metastases were: nine mammary tumors (one with less than 1% tumor cells positive, eight negative), four pulmonary tymors (all negative) and four colonic tumors (one with more than 50% positive tumor cells, onw [*sic*] with less than 1% tumor cells positive, two negative)."

surface and sometimes in the nucleus, but no cytoplasmic staining was seen as the MN protein was identified by the Applicants to be a transmembrane protein.

The Oosterwijk references cannot anticipate or render obvious the claims of the present application since the G250 antigen is, not only not identified by any biochemical characteristics, but also whatever characterization that could be deduced about the G250 antigen from the G250 Mab's immunoreactivity reported in the Oosterwijk references are very different from the actual characterization of the MN protein disclosed and claimed in the present application. One of skill in the art relying upon Oosterwijk would not associate the G250 antigen with the MN protein or any MN-related invention, as the claimed anti-idiotype antibodies but mimic the MN protein of SEQ ID NO: 2. Further, the Oosterwijk et al. 1986 and 1988 references are evidence of the nonobviousness of the instant invention.

Raychaudhuri et al. '202 Patent

The Raychaudhuri et al. '202 patent contains no disclosure concerning the MN protein, and certainly contains no disclosure concerning an anti-idiotype antibody to an antibody that specifically binds to the MN protein of SEQ ID NO: 2. The Raychaudhuri et al. '202 patent can add nothing to the disclosures of the Oosterwijk et al. 1986 and 1988 references concernng the potential identity of the G250 antigen and/or of the biochemical characteristics or accurate immunostaining patterns of the G250 mab.

In fact, the Raychaudhuri et al. '202 patent supports the nonobviousness of the instant invention, emphasizing the importance of characterizing the antigen that the anti-idiotypic antibody mimics. According to the methods of the Raychaudhuri et al. '202 patent, one of skill in the art could not confirm that they had prepared an anti-idiotype antibody with an internal image that mimicked an epitope of the MN protein of SEQ ID NO: 2, without knowledge of the structure, molecular weight or other biochemical properties of the MN protein. Since the Oosterwijk et al. 1986 and 1988 references provide no biochemical characteristics of the G250 antigen, and not even the fact whether said G250 antigen were a protein or not, and most certainly nothing about its amino acid sequence, the Raychaudhuri et al. '202 patent in combination with those

Oosterwijk references emphasizes the improbability that anyone of skill in the art could have prepared the claimed anti-idiotype antibodies based on the Oosterwijk et al. disclosures, and the myriad of potential RCC-preferential antigens to which the second antibodies could specifically bind. Applicants respectfully conclude that the Raychaudhuri et al. '202 patent alone or in combination with either or both of the Oosterwijk references cannot render the instantly claimed invention obvious but in fact provides evidence of the non-obviousness of the claimed invention.

V. First 35 USC § 103(a) Rejection (Section 13 of the Office Action)

> Claims 22, 30, 36-38, 42, 43, 46-48 and 53-55 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Oosterwijk et al [a](WO 88/08854, Publication date 11/17/1988, Ids 10/19/2001) as evidenced by Uemura et al (British Journal of Cancer, 81(4): 741-746, 1999 . . .) and Pastorek et al (Oncogene, 9: 2877-2888, 1994 . . .) and in view of Raychaudhuri et al (US Patent 5,270,202, 3/12/91, cited previously).

[Office Action, page 12, Section 13.] Applicants respectfully traverse, first relying on their prior responses ("prior responses" – those dated July 22, 2004; April 11, 2005; and June 13, 2005), respectfully arguing that the Examiner is confusing the Oosterwijk et al. publication disclosing an entity designated "the G250 Mab", with public use and availability of an actual three-dimensional compound, the G250 Mab. Without such public use and availability, which was not provided until the deposit of the G250 hybridoma on September 11, 2001, one of skill in the art could not have produced an anti-idiotype antibody mimicking an epitope of the MN protein and would have had no means of determining that the G250 antigen (which the Oosterwijk 1986 and 1988 references suggest could be a protein), was in any way associated with the MN protein which has the amino acid sequence of SEQ ID NO: 2. The Oosterwijk et al. references teach away from all MN-related inventions, and therefore cannot render the instant claims obvious.

In addition, Oosterwijk et al. [a] did not isolate or describe the G250 antigen, and any information provided regarding the "Mab G 250" taught away from

identifying the MN protein with the G250 antigen, as detailed in Applicants' previous responses [for example, the response dated July 22, 2004 at page 44, 2nd paragraph to page 45, 1st full paragraph.] Moreover, without the hindsight provided by the cited Pastorek et al. and Uemura et al. references (published long after the earliest priority date of the instant application, March 11, 1992), the cited Raychaudhuri et al. patent ("the '202 patent") supports the non-obviousness of the instant invention, emphasizing the importance of characterizing the antigen that the anti-idiotypic antibody mimics. Applicants respectfully maintain that one of ordinary skill in the art, following the conventional methods used by Oosterwijk et al. [a] and using renal cell carcinomas as a source of antigen, would not have "a reasonable expectation of success" in producing anti-idiotype antibodies that mimic the MN protein expressed by renal cell carcinomas, as evidenced by the **multitude of different antibodies to RCC-preferential antigens (other than MN protein)** that were produced by at least eight RCC laboratories at the time of the instant invention, and the notable absence of production of antibodies to MN protein by those same laboratories.

The Office Action states at page 15 that

> [O]ne of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to have produced anti-idiotypic antibodies of the beta type to an antibody that specifically binds the G 250 protein produced according to the teachings of Oosterwijk et al [a] for RCC therapy. . . . [T]he teachings of Oosterwijk et al [a] indicate success in producing a monoclonal antibody that specifically binds the G 250 protein using a **homogenate of renal cell carcinomas as immunogen** and according to Raychaudhuri, "methods for generating such anti-idiotypic antibodies are well known to those of skill in the art" . . .

[Emphasis added.]

There was no knowledge that was within the level of ordinary skill in the art, at the time the claimed invention was made, to provide a "reasonable expectation of success" of preparing antibodies that recognize the MN protein rather than another antigen expressed by renal cell carcinomas. Those of skill in the art at the time of Oosterwijk et al. [a] referred to the "**high level of heterogeneity associated with**

human renal cell carcinoma" [Abstract, Blouin et al., Exp. Pathol., 36(3):147-63 (1989) (copy of abstract enclosed); emphasis added.] In the 1986 Oosterwijk reference cited in the second 103(a) rejection (infra), Oosterwijk et al. state on page 493 (col. 2) that "endogenous or exogenous retrovirus expression in RCC . . . may explain the relatively **large number of new antigens in RCC**." [Emphasis added.] The described process for the production of a G250 hybridoma does not enable one of skill in the art to determine, to which of the huge number of antigens in RCC cell homogenates the secreted G250 Mabs are specific.

Oosterwijk et al. [a] provided no indication of which parameters were critical to prepare antibodies to the G250 antigen, instead of antibodies to one **of at least thirteen other RCC-preferential antigens** (S22, D5D, B7, C8, D8, E6, DAL-K20, DAL-K29, DAL-K45, KRC-1, KRC-2, KRC-3, and A25) which were isolated by six of at least eight other laboratories[2] studying RCC antigens, using techniques comparable to the conventional techniques followed by Oosterwijk et al. (initial immunization of mice with fresh RCC tumor cells or homogenates, or with RCC cell lines, prior to preparation of hybridomas). Therefore, at the time of the instant invention the probability that one of skill in the art using the techniques of Oosterwijk et al. would isolate a monoclonal antibody to MN protein was at best 1 out of 14 (one anti-MN Mab, G250, out of at least fourteen RCC-preferential antibodies), or 7%. That optimistic 7% probability [only based on a limited search and could be a much lower probability] in view of the potential myriad of RCC-preferential antigens, is not a "reasonable expectation of success". Furthermore, the probability that one of skill in the art would have been able to confirm according to the methods of Raychaudhuri et al. that they had prepared an anti-idiotype antibody with an internal image that mimicked an epitope of the G250 protein or the MN

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2. Klingel et al., Am. J Kidney Dis., 19(1):22-30 (1992) (abstract enclosed); Ebert and Bander, Immunol. Ser., 53:469-83, (1990) (abstract enclosed); Terashima et al., Nippon Hinyokika Gakkai Zasshi, 80(6):838-46, (1989) (abstract enclosed); Blouin et al., Exp. Pathol., 36(3):147-63 (1989) (abstract enclosed); Tokuyama and Tokuyama, Hybridoma, 7(2):155-65 (1988) (abstract enclosed); Luner et al., Cancer Res., 46(11):5816-20 (1986) (article enclosed with 10/17/01 IDS); Vessella et al., Cancer Res., 45(12 Pt 1):6131-6139 (1985) (article enclosed with 10/17/01 IDS); and Schärfe et al., Eur. Urol., 11(2):117-120 (1985) (article enclosed).

protein, without knowledge of the structure, molecular weight or other biochemical properties of the MN protein, and without availability of the G250 Mab, was **zero**.

According to the cited Raychaudhuri et al. '202 patent, the process of generating internal image anti-idiotype antibodies is described as conventional in the art:

> (1) an antibody is made against an antigen or an infectious agent (this antibody is called an "Ab1"); and, (2) anti-idiotypic antibodies ("Ab2s") are made against these Ab1s. These antimaids (Ab2s) are screened for the expression of idiotypes that mimic the immunological properties of the initial antigen (such as that expressed by a tumor or infectious agent). This screening consists of inhibiting the Ab1-Ab2 interaction by the original antigen and the biological testing of the anti-idiotypes (Ab2) as a surrogate antigen in vivo.

[Raychaudhuri et al., U.S/ Patent 5,270,202, col. 2, line 66 to col. 3, line 8; emphasis added.] Applicants respectfully ask, how was the screening step for internal image anti-idiotypic antibodies (which required characterization of the original antigen) to be performed at the time of the invention? Raychaudhuri et al. required that the anti-idiotypic antibody was capable of reacting with an idiotope, wherein the idiotope was capable of reacting with a specific epitope of a specific antigen (the MPG antigen) [Raychaudhuri et al., col. 4, lines 36-45.] Using only what was known at the time of the instant invention (without knowledge of the structure of the MN protein or availability of the G250 Mab), how would one of skill in the art been able to distinguish an anti-idiotypic antibody of the beta type (Ab2 beta) to an antibody which specifically binds the MN protein, from an anti-idiotypic antibody which mimics any other of the RCC-preferential antigens?

Only in 1997, years after the priority date of the present application, and further years after the M75 Mab of Claim 23 of the present application became publicly available from an international depository, did the inventors/authors of Oosterwijk et al. and Uemura et al. report that the G250 antigen "is identical to MN, a tumor-associated antigen identified in cervical carcinoma (Pastorek et al. 1994). This antigen (G250, MN) is a transmembrane glycoprotein of 54/58 kDA and detectable in several types of malignancies. . . ." [Uemura, J. Urology 157: 377 (1997); emphasis added.] As argued

by Applicants in their previous responses, the antigen G250 is not reproducibly described by Oosterwijk for one skilled in the art and therefore not sufficiently disclosed. In the Oosterwijk et al. 1986 cited reference (infra), Oosterwijk et al. distinguish the G250 Mab from the other RCC-specific Mabs that do not react with normal renal tissue only by the staining patterns of the various Mabs. For example, Vesella et al.'s D5D Mab stained 14 of 19 RCC (74%) in contrast to the G250 Mab which stained 53 of 55 RCC (98%), and Schärfe's Mabs, although staining as high a percentage of RCC as the G250 Mab, do no stain sarcomatous RCC in contrast to the G250 Mab [see Oosterwijk et al. 1986, p. 493, top of 2nd col.]. However, the immunoreactivity of the G250 Mab as reported by Oosterwijk is distinctly different from the immunoreactivity of the MN-specific antibodies M75 and M12 of the present invention, as recited in Applicants' previous responses.

In addition, three other RCC laboratories isolated seven other additional RCC-preferential monoclonal antibodies, but apparently none specific to the MN protein. In 1988, Tokuyama and Tokuyama [Hybridoma, 7(2):155-65 (1988); abstract enclosed] isolated three monoclonal antibodies (KRC-1, KRC-2, KRC-3) which reacted specifically with a subset of human RCC, but did not react with other tumor cell lines, tumor and normal tissues including kidney. Tokuyama and Tokuyama stated that "molecular properties of the antigens appeared to be different from those of previously reported RCC-associated antigens", with molecular weights of 135 kD and 1200 kD (Abstract, Tokuyama and Tokuyama 1988). Another laboratory, Luner et al. [Cancer Res., 46(11): 5816-5220 (1986) (article provided in 10/17/01 IDS)], prepared three monoclonal antibodies (DAL-K20, DAL-K29, DAL-K45) which reacted with antigens (molecular weights of 118 kD, 150 kD, and 177 kD) present in most human RCCs but restricted in their expression in normal adult tissues. A sixth laboratory, Terashima et al. [Nippon Hinyokika Gakkai Zasshi, 80(6): 838-46 (1989) (abstract enclosed)], isolated a monoclonal antibody preferentially reactive to RCC cell lines designated "A25", which also reacted with normal proximal kidney tubules. No one in the Tokuyama, Luner or Terashima laboratories apparently isolated the MN protein or a monoclonal antibody thereto, although all were presumably motivated to find RCC-specific antigens.

Oosterwijk et al. in "Immunohistochemical Analysis of Monoclonal Antibodies to Renal Antigens: Application in the Diagnosis of Renal Cell Carcinoma," Am. J. Pathol., 123(2): 301-309 (May 1986) (IDS submitted on 10/17/01) at page 307 (2nd col.) discuss Mabs to RCC — RC3, RC 38, RC 69 and RC 154 – which Mabs are claimed in Oosterwijk et al. [a]. That article refers to "[o]ther investigators [who] have also described Mab's with a high specificity for RCC . . . [citations admitted]," and admit that "[a] comparison between the Mab's described in this study with Mab's against renal antigens described by others is difficult, partly because of different assay methods." [Emphasis added.] If it is difficult to distinguish RCC-specific Mabs from one another by their staining patterns, what would the staining pattern of a RCC-specific Mab suggest about another Mab that was known not to be RCC-specific and to have otherwise very different immunoreactivity than that reported for the RCC-specific Mab?

At page 17, the Office Action states that "applicant is reminded that obviousness only requires a reasonable expectation of success, obviousness does not require absolute predictability." Applicants respectfully submit that at the time of the instant invention, one of skill in the art attempting to prepare anti-idiotype antibodies mimicking the "G250 antigen" of WO 88/08854 would **far more likely than not** have prepared an anti-idiotype antibody **mimicking a different RCC-specific antigen**, such as Ueda's "S22", Vesella's "D5D", and Schärfe's "B7", "C8", "D8" and "E6", among the other numerous antigens that were isolated by the at least nine laboratories worldwide (including Oosterwijk et al.) attempting to isolate RCC-specific antigens, instead of isolating anti-idiotype antibodies against "G250 Mab", without more information about the nature of the G250 antigen. One would expect that if those RCC laboratories had anticipated or reproduced the findings of Oosterwijk et al. [a] or [b], those laboratories would have reported their findings rather than cover them up. Why did none of those eight additional RCC immunology laboratories mentioned above (other than Oosterwijk et al.) isolate monoclonal antibodies to MN protein before the instant invention was made (March 11, 1992), if there was a "reasonable expectation of success" in doing so when the skilled artisan prepared RCC-preferential Mabs by injecting mice with RCC cells or homogenates?

Conclusion

Applicants respectfully conclude neither Oosterwijk alone or in view of Raychaudhuri renders the instantly claimed invention obvious, but instead as explained above is evidence of the nonobviousness of the instant invention. Further, as argued above and in Applicants' previous responses, the Pastorek et al. 1994 and Uemura et al. 1999 references are not prior art to the instant claims, and their application to the subject rejection would be impermissible hindsight. Applicants respectfully request that the Examiner reconsider the instant rejection in view of the above remarks, and withdraw the subject 103(a) rejection.

VI. 35 USC § 103(a) (Section 14 of the Office Action)

Claims 22, 30, 36-38, 42, 43, 46-48 and 53-55 stand "rejected under 35 U.S.C. 103(a) as being unpatentable over Oosterwijk et al [b](International Journal of Cancer, 38:489-494, 1986, Ids 10/19/2001) as evidenced by Uemura et al ...and Pastorek et al. . . . and in view of Raychaudhuri et al (U.S. Patent 5,270,202, 3/12/93, cited previously)." [Office Action, page 18, section 14.] The Office Action further states beginning at the bottom of page 18:

> Oosterwijk et al[b] teach a method for producing monoclonal antibodies . . . against the G 250 antigen present on RCC and absent from normal kidney tissue. . . . As evidenced by Uemura et al the G 250 antigen is identical to MN protein. . . and as evidenced by Pastorek et al the G 250 antigen is encoded by SEQ ID NO:1. Thus, as evidenced by Uemura et al and Pastorek et al the G 250 antigen is identical to the MN protein of the present claims and is necessarily encoded by the nucleic acid of SEQ ID NO:1. Oosterwijk et al [b] do not specifically teach an anti-idiotype antibody to an antibody that specifically binds the MN protein. This deficiency is made up for in the teachings of Raychaudhuri.

Applicants respectfully traverse this rejection, first relying on their previous responses (dated July 22, 2004; April 11, 2005; and June 13, 2005), and also relying on arguments presented in the previous section, noting that most of the disclosure of the Oosterwijk et al. 1986 article (International Journal of Cancer) is contained in the Oosterwijk et al application (WO 88/08854).

As mentioned in the response to the first 103(a) rejection (supra), Oosterwijk et al. state on page 493 (col. 2) that "endogenous or exogenous retrovirus expression in RCC . . . may explain the relatively large number of new antigens in RCC." [Emphasis added.] The described process for the production of a G250 hybridoma does not enable the skilled artisan to determine, to which of the huge number of antigens in RCC cell homogenates the secreted G250 mabs are specific. Conventional methods were used to produce the G250 hybridoma, that secretes the G250 Mabs as described in Example 1 of Oosterwijk: a mouse was immunized with cell homogenates from primary RCC lesions. At any one time, perhaps about 100,000 proteins are being expressed in a cell, and thousands of proteins are being expressed on the surface of a cell. Oosterwijk 1986 supports that there are a wide variety of Mabs that stain RCC but do not stain normal kidney tissue. One of skill in the art would had have a low expectation of success in producing anti-idiotype antibodies mimicking the "G250 antigen" based on only the disclosures of Oosterwijk et al. [b] and Raychaudhuri et al. and without the impermissible hindsight of Pastorek et al. and Uemura et al. Oosterwijk et al. in view of Raychaudhuri et al. cannot anticipate or render obvious the claims of the present application since one of ordinary skill in the art would not have had a reasonable expectation of success at the time the invention was made to have produced anti-idiotypic antibodies of the beta type to an antibody that specifically binds the G250 protein produced according to the teachings of Oosterwijk et al. [b] for RCC therapy. As evidenced by the large number of RCC-specific antibodies prepared in eight different laboratories at the time of the invention, and the lack of isolation of antibodies to MN protein in the same laboratories, it was highly unlikely that one of skill in the art would have been successful in preparing antibodies specific to MN protein without much more direction than that provided in Oosterwijk et al. [b]. Furthermore, Raychaudhuri et al. teaches the necessity of screening internal image anti-idiotype antibodies using the original antigen, and therefore teaches that the skilled artisan must have characterized the original antigen.

As argued in the preceding 103(a) response (supra), Applicants respectfully submit that neither Pastorek et al. 1994 nor Uemura et al. 1999 can be

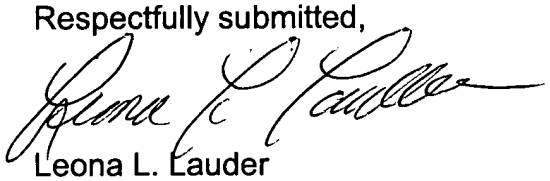
applied as a reference against the subject claims, as they are not prior art, and their application in the 103(a) rejection would constitute impermissible hindsight.

Applicants respectfully conclude that Oosterwijk et al. [b] in view of Raychaudhuri fail to render the instantly claimed invention obvious, but instead as explained above are evidence of the nonobviousness of the instant invention. The Oosterwijk et al. references teach away from MN-related inventions and therefore cannot render the claimed invention as obvious. Further, the Uemura et al. 1999 and Pastorek et al. 1994 references cannot be cited against the instant application, as they provide impermissible hindsight. Applicants respectfully request that the Examiner reconsider the instant rejection in view of the above remarks, and withdraw the second 103(a) rejection.

CONCLUSION

Applicants respectfully conclude that the claims as amended are in condition for allowance, and earnestly request that the claims as amended be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,



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